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Evidence Summary Report 13-1 EDUCATION AND INFORMATION 2013

The Treatment of Lymphedema Related to Breast Cancer

Kligman L, Wong R, Johnston M, Laetsch N,
and members of the Supportive Care Guidelines Group

Report Date: August 22, 2003

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The Treatment of Lymphedema Related to Breast Cancer
Evidence Summary Report #13-1

Kligman L, Wong R, Johnston M, Laetsch N, and members of the Supportive Care Guidelines Group

Report Date: August 22, 2003

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base a practice guideline.

SUMMARY

Question

What are the treatment options for women with lymphedema following treatment for breast cancer?

Target Population

Women with lymphedema following treatment for breast cancer whose symptoms warrant treatment.

Methods

Searches of the MEDLINE (May 2000 through March 2002), CANCERLIT (May 2000 through March 2002) and Cochrane Library (2002, Issue 1) databases were conducted to supplement the evidence reviewed by the Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer for their published practice guideline (Harris SR, Hugi MR, Olivotto IA, Levine M, for the Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 11. Lymphedema CMAJ 2001;164:191-9.)

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative's Supportive Care Guidelines Group. This evidence summary report has been reviewed by the Supportive Care Guidelines Group, which includes palliative care physicians, nurses, radiation oncologists, psychologists, medical oncologists, a chaplain, an anesthetist, a surgeon, methodologists, and administrators. A draft document was also shared with the provincial Breast Cancer Disease Site Group for their input.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the evidence summary report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each report. The process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original evidence summary.

Key Evidence

- One small randomized trial (N=25) detected an incremental benefit when use of a compression garment was added to self-massage therapy.
- Pneumatic compression, when compared with no intervention, was not associated with a significant improvement of the magnitude that the randomized trial was powered to detect. However, the direction of the observed response rates and changes in arm volume favoured pneumatic compression.
- None of the other, more aggressive approaches were found to have benefits when compared with less aggressive controls in three randomized trials, but there are no data regarding their effectiveness when compared with no intervention.
- In terms of medical therapies, there was contradictory evidence about the role of coumarin in the management of lymphedema. Two randomized trials used very similar study designs but arrived at opposite conclusions. The role of O-β-rutosides is promising but requires further study in randomized trials. The data from a randomized trial do not suggest that Daflon has clinically significant activity in the treatment of lymphedema.

Opinions of the Supportive Care Guidelines Group

The lack of sufficient high quality evidence precludes definitive recommendations from being made. Instead, the Supportive Care Guidelines Group offers the following opinions based on the evidence reviewed:

- There is some evidence which suggests that physical therapies such as compression therapy and manual lymphatic drainage may improve established lymphedema but further studies are needed.
- There is no current evidence to support the use of medical therapies, including the use of diuretics, in the management of lymphedema.
- Additional efforts to define relevant clinical outcomes for the assessment of patients with lymphedema would be valuable.
- The Supportive Care Guidelines Group endorses the recommendations from the Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. The use of compression garments, as recommended in the national guideline, is consistent with what is commonly practiced clinically.
- The recommendations are appropriate for patients with more than mild lymphedema, where the signs and symptoms are considered significant from the patients' perspective.
- There is insufficient evidence to support an evidence-based recommendation on which to base a practice guideline for the treatment of lymphedema. Available studies were uniformly small, and underpowered limiting the power of inference.
- Compression garments should be worn from morning to night and removed at bedtime. Patients should be advised that lymphedema is a lifelong condition and that compression garments must be worn on a daily basis. Patients can expect stabilization and/or modest improvement of edema with the use of the garment in the prescribed fashion.

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The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.
Visit http://www.cancercare.on.ca/access_PEBC.htm for all additional Practice Guidelines Initiative reports.

PREAMBLE: About Our Evidence Summary Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by Disease Site Groups of the PGI using the Practice Guidelines Development Cycle methodology.[1]

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base a practice guideline. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. For example, the evidence comes from uncontrolled studies, from studies with control groups that are not relevant to current practice in Ontario, or from subgroup analyses, or the evidence consists solely of preliminary results from ongoing trials. The Program in Evidence-based Care will monitor the scientific literature and will develop a practice guideline on this topic when more evidence becomes available.

This evidence summary report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, community representatives, and Cancer Care Ontario executives. Formal approval of an evidence summary by the Coordinating Committee does not necessarily mean that the evidence summary has been adopted as a practice policy of CCO. The decision to adopt an evidence summary as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:
[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al.. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

For the most current versions of the evidence summary reports and information about the PGI and the Program, please visit our Internet site at:
http://www.cancercare.on.ca/access_PEBC.htm.
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Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence summary is expected to use independent medical judgement in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

FULL REPORT

I. QUESTION

What are the treatment options for women with lymphedema following treatment for breast cancer?

II. CHOICE OF TOPIC AND RATIONALE

Lymphedema is a source of major morbidity for men and women living with cancer, either as a direct result of the tumour or as a side-effect of treatment. Quality of life, in both a physical and emotional sense, can be dramatically affected.

In Ontario, it is estimated that there will be 6,200 new cases of breast cancer in 2001. The exact incidence of lymphedema has been difficult to establish given the variability in how lymphedema is defined, the degree to which it is clinically relevant, the extent of surgery or radiotherapy, and potential reporting bias (1-4). Estimates of lymphedema incidence among breast cancer patients include 10% from surgery alone, increasing to 20-30% when the treatment includes radiation therapy (1-4). This means that in Ontario between 600 and 1,800 women diagnosed with breast cancer in 2001 can expect to develop lymphedema at some point during their lives. The risk of developing lymphedema following management of breast cancer is related to the type of treatment received, such as axillary lymph node dissection (versus use of sentinel lymph node biopsy) and nodal irradiation. While the majority of women with breast cancer-related lymphedema will have mild swelling that may never require treatment, a significant subset of patients will have clinically significant lymphedema that would benefit from and warrant consideration for active intervention. A prosthesis can camouflage an amputated breast; a swollen arm is much more difficult to hide. Information and resources for treatment are limited and may be difficult to access. Problems associated with lymphedema are economic as well as cosmetic: public and private health insurance plans usually cover only a limited proportion of the costs associated with ongoing management.

In this report, we present a summary and interpretation of the evidence that clinicians may use as an aid to providing evidence-based care for lymphedema.

III. METHODS

Evidence Summary Development

This evidence summary report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (5). Evidence was selected and reviewed by two members of the PGI's Supportive Care Guidelines Group (SCGG). This evidence summary report has been reviewed by the SCGG, which includes palliative care physicians, nurses, radiation oncologists, psychologists, medical oncologists, a chaplain, an anesthetist, a surgeon, methodologists, and administrators. A draft document was also shared with the provincial Breast Cancer Disease Site Group (DSG) for their input.

The evidence summary report is a convenient and up-to-date source of the best available evidence on the treatment of lymphedema related to breast cancer, developed through a systematic review, evidence synthesis, and input from practitioners in Ontario. In contrast to the practice guidelines, the body of evidence in an evidence summary is less mature and is comprised of data primarily from non-randomized controlled trials or data available only in abstract form. This precludes the development of definitive recommendations and instead, opinions of the SCGG are offered. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the evidence-summary-in-progress report, the interpretation of the available evidence, and whether there is a need to develop an evidence-based practice guideline when sufficient evidence is available. Final approval of the evidence summary was obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each evidence summary report. The process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original evidence summary.

Literature Search Strategy

When they undertook the development of this evidence summary, the SCGG was aware of a recently completed Canadian practice guideline by the Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer (6). This national guideline was based on a systematic review of the English-language literature found by searches of MEDLINE (1966 to April 2000) and CANCERLIT (1985 to April 2000), and references cited in reviews and textbooks. The guideline authors reported that a "nonsystematic review of the breast cancer literature to October 2000 also took place".

A search for new evidence was conducted by the Provincial SCGG for the period from May 2000 through March 2002. MEDLINE (Ovid), CANCERLIT (Ovid), HealthStar, CINAHL, PREMEDLINE, and the Cochrane Library (2002, Issue 1) were searched using the exploded subject headings 'breast neoplasms', 'lymphedema' and 'clinical trials', the text words 'breast', 'mammary', 'carcinoma', 'cancer', 'neoplasm', 'lymphedema' and 'lymphoedema', and the publication type 'clinical trial'. Reference lists in papers found by the update search were reviewed to identify further trials. The Canadian Medical Association Infobase (http://www.cma.ca/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) and other web sites were searched for evidence-based practice guidelines.

Study Selection Criteria

Inclusion Criteria

Studies were eligible for inclusion in the evidence summary if they met all of the following criteria:

1. They were randomized trials or systematic reviews of randomized trials of treatments for lymphedema related to treatment for breast cancer.
2. They measured the effect of therapy for lymphedema on arm volume, symptom control, quality of life, or cosmetic results.

Exclusion criteria

Because resources available for translation were limited, study reports published in languages other than English were excluded.

Outcomes of interest

The primary outcome of interest was the proportion of patients with reduction in lymphedema. Secondary outcomes included: difference in arm volume between the patient's treated and control arm, reduction in symptoms associated with lymphedema, quality of life, and adverse effects of treatment.

Synthesizing the evidence

It was the original intention to consider using a meta-analysis approach to summarize the data. However, upon reviewing the available data, pooling was not felt to be appropriate for the following reasons:

- Physical and medical therapies need to be considered separately.
- Of the physical therapy trials, no two studies compared the same or similar types of physical therapy.

There was significant variability on how outcomes were assessed across the studies. The randomized studies were categorized by the interventions being evaluated. A detailed discussion of each study and the outcomes of interest are presented below.

IV. RESULTS

Literature Search Results

Interventions evaluated in randomized trials included:

Compression bandaging

This is usually the first therapy used to reduce edema. Multi-layered "short-stretch" bandages are used in the reduction phase of treatment. These bandages provide low compression at rest and enhance the effect of muscular activity on the clearance of lymphatic fluid from the limb.

Compression garment

A compression sleeve may be used to reduce edema in mild cases or to maintain the reduction achieved by compression bandaging or other volume-reducing techniques described below. It is custom fitted to apply external pressure in the range of 20–60 mmHg. These garments typically cover the arm from wrist to mid-humerus and may be prescribed with an attached gauntlet or separate glove. They are usually removed overnight.

Manual lymphatic drainage

Manual lymphatic drainage is gentle massage of the skin surface performed by a specially trained massage therapist. The massage typically starts at the trunk, bordering the edematous area, and slowly moves more distally, ending with the hand and fingers. The aim is to stimulate and direct lymphatic flow from areas of stasis to functioning lymphatics. It is the only treatment that moves fluid out of the upper arm and shoulder where it accumulates above the compression bandage or sleeve.

Comprehensive lymphedema management program/complex physical therapy/complex decongestive therapy (CDT)/complete decongestive therapy

These therapies include all of the above-mentioned treatments in an intensive regimen that includes patient education, meticulous skin hygiene, manual lymph drainage, bandaging, exercises, and compression garments. Patients are typically seen daily for approximately six weeks and then fitted with a compression garment.

Pneumatic compression pump

Pneumatic devices are used to administer pressure on the involved arm, using either a single chamber or multi-chamber sleeve. The pump is set to deliver a prescribed amount of intermittent pressure. The multi-chamber sleeve is able to deliver the pressure in a sequential fashion. Pumps are available through some physiotherapists, or patients can buy or rent them from a home health supply company. The pump is used for several hours a day, and the patient

must apply compression in the form of bandaging or a sleeve following a pump-down session. A course of treatment lasts from a few days to four weeks. The amount of compression used must be prescribed by a physician.

Electrically stimulated lymphatic drainage

A less commonly used intervention involves a sequence of electrical impulses delivered through electrodes placed over lymphatic stations or motor points between the supraclavicular region and the wrist.

Medical therapies

Treatment with oral drugs, such as benzopyrones, that have the potential to stimulate proteolysis by tissue macrophages have been evaluated in clinical trials.

There were no other studies meeting the eligibility criteria that addressed other common clinical recommendations such as the use of diuretics, general skin care, or other non-medical therapies (e.g. magnetic therapy or infrared garments).

Practice Guidelines

The Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer has published a national guideline to provide an evidence-based approach to the management of lymphedema in women who have been treated for breast cancer in Canada (6). The treatment recommendations in the guideline were based on evidence from clinical studies, ranging from case series to randomized trials, and on input from physical therapists, surgeons, radiation oncologists, medical oncologists, and women with lymphedema. Practical tips, based on consensus and current clinical practice patterns were also included in the recommendations. In addition, suggestions were made on the measurement of lymphedema and the relevance of addressing pain and psychosocial issues. Future research directions were also discussed.

Several other groups have produced clinical practice guidelines on lymphedema (7-10), but these were not based on systematic reviews of the evidence.

Systematic Reviews

Four systematic reviews were found (11-14), but they included much smaller numbers of trials than the national practice guideline described above (6). An additional systematic review (15) was found, which included only three of the six trials evaluating physical therapy and only three of the four trials of medical therapy included in this evidence summary report. Two Cochrane systematic review protocols were identified; one addressed lymphedema secondary to treatment of breast cancer (16), and the other examined the effect of physical treatment programs on edema in lymphedematous limbs (17). As these are in protocol form, no results are available to date.

Randomized Controlled Trials

Ten randomized controlled trials (RCT) fulfilled the eligibility criteria and form the basis of this evidence summary (18-27). Seven of these trials were included in the national guideline (20-26), and three were identified by update searches (18,19,27). The characteristics of the RCTs are described below and are summarized in Tables 1 and 2; study results are presented in Table 3.

Patient Characteristics

All studies included patients with established arm lymphedema, with the exception of one prophylactic study in women undergoing mastectomy and lymph node dissection (27). Two studies included patients with leg edema but presented results separately for patients with

lymphedema related to breast cancer (24,25). Definitions of lymphedema were variable, and two studies did not provide a definition (18,19). The duration of established lymphedema prior to entering the study was different for the physical and medical therapy trials. The median or mean duration of lymphedema for the physical therapy studies ranged from 6.5 to 14.5 months, while for medical therapies, they ranged from 3.2 years to 8 years.

Study Intervention

The range of interventions included in the RCTs is summarized in Table 1. There were six randomized trials evaluating physical therapies (18,20-23,27) and four addressing medical therapies (19,24-26). One study employed physical therapy as a preventive therapy between surgery and commencement of radiotherapy (27), while the remaining nine studies used therapy for symptomatic lymphedema.

Of the physical therapy studies, two incorporated a no-intervention control arm (21,27) and four others employed active controls, comparing two different forms of physical therapy (18,20,22,23). None of these trials used blinded outcome assessments. All four studies of medical therapy were placebo-controlled and employed a crossover design with no washout period (19,24-26).

Duration of Intervention

Physical therapy for the treatment of established lymphedema was generally short, ranging from two weeks (20,22) to two months (23). In the prophylactic therapy study by Pecking et al., therapy was given between surgery and the start of radiotherapy (27). The intention was to give medical therapy for six months in each phase of the cross-over trials (19,24-26).

Duration of Follow-up

For the five studies examining physical therapy for established lymphedema, the first assessment for response was performed at varying intervals (range from two weeks to two months) from entry into the trial (18,20-23). Follow-up data beyond the duration of treatment was available from three studies (18,20,23). For the single prophylactic study, first response was measured on day five, and some patients were followed for five years after treatment (27).

For the four studies of medical therapy, first response was measured at one month (25), two months (26) or six months (19,24). Long-term follow-up data, beyond the duration of the study intervention, were not collected.

Sample Size

Studies were generally small and underpowered. Sample sizes ranged from 25 to 104.

Table 1. Summary of interventions evaluated in randomized controlled trials of therapy for lymphedema related to breast cancer. (For details on interventions, see Table 3.)

Trial (reference)	Placebo control	No-treatment control	Exercise + self-massage therapy	Elastic sleeve/ compression garment	Manual lymph drainage	Pneumatic compression pump	Electrically stimulated lymphatic drainage	Medical therapy
Treatment								
Hornsby 1995 (18)			+	+				
Anderson et al. 2000 (20)				+	+			
Dini et al. 1998 (21)		+				+		
Johansson et al. 1998 (22)					+	+		
Bertelli et al. 1991 (23)				+			+	
Casley-Smith et al.1993 (24)	+							+
Pecking et al. 1997 (19)	+							+
Piller et al. 1998 (25)	+							+
Loprinzi et al. 1999 (26)	+							+
Prevention								
Pecking et al. 1988 (27)		+		+	+			

Outcome Assessment

The methods by which outcomes are measured can have a direct impact on the validity and reliability of the outcome measure. Outcome measurement for the included studies is discussed below.

Lymphedema

Lymphedema and its response to therapy was measured in a variety of ways.

Four trials measured arm volume using the water-tank-submersion method (18,22,24,25). Six others estimated arm volume by taking limb-circumference measurements at a number of sites (between five and eight) (19-21,23,26,27). The amount of edema was determined by calculating the difference in volume between the edematous and normal arm. Outcomes were expressed as either an absolute difference in size between the affected and the contralateral arm (21,22,26) or as the relative change in the amount of edema (reported as a percentage of baseline) (19,20,23-25).

Three trials reported response rates: that is, the percentage of patients who experienced a reduction in arm size (18,21,23). The definition of response was “any reduction in arm volume” in the trial by Hornsby (18) and “a reduction in volume (delta) of at least 25%” in the trials by Dini et al. and Bertelli et al. (21,23).

The proportion of patients developing lymphedema was used as an outcome measure in the prophylactic study by Pecking et al. (27). Lymphedema was defined as an increase in arm circumference of 2 cm or more, but the location where this was measured was not stated (27).

Symptoms

Six studies reported on symptoms associated with lymphedema (swelling, discomfort, cramping, heaviness, pain, tightness, aching, paresthesia, inflammation, dryness, impaired function, and decreased mobility), and some asked about general well being (19,20,22,24-26). Scales included better/same/worse (20,24,25), none/mild/moderate/severe (26), and visual analogue scales (19,22).

Quality of life

None of the randomized trials evaluated the effect of therapy on quality of life.

Adverse effects

None of the physical therapy studies reported on the adverse effects of therapy. Two of the four medical therapy studies reported adverse effects (19,26) but no grading classification was used.

Table 2: Characteristics of randomized trials of therapy for lymphedema.

Trial	Experimental treatment	N	Control treatment	N	Duration of therapy (weeks)	First outcome assessment (week)	Subsequent outcome assessments	Definition of lymphedema	Duration of lymphedema (median)
Physical therapy as treatment for lymphedema									
Hornsby 1995 (18)	Elastic compression sleeve worn day & night + exercise & self-massage	14	Exercise & self-massage	11	4-28	4	8 -28 weeks	Not reported	Not reported
Andersen et al. 2000 (20)	Manual lymphatic drainage 8 times over 2 weeks + daily self-massage + standard therapy	20	Standard therapy: compression garment, education, exercises	22	2	4	3 -12 months	- Difference in volume between arms ≥200 ml or in circumference≥2 cm (at 1 point) - Difference in volume ≤30%	14.5 months
Dini et al. 1998 (21)	Intermittent pneumatic compression (constant pressure of 60 mmHg) 5Xweek for 2 weeks, repeated after 5-week break	40	No treatment	40	9	9	none	Difference between arms in circumference >10 cm (totalled over 7 points)	6.5 months (mean)
Johansson et al. 1998 (22)	Sequential pneumatic compression (40-60 mmHg) 5Xweek for 2 weeks + compression sleeve	12	Manual lymphatic drainage 5Xweek for 2 weeks + compression sleeve	12	2	2	none	>10% difference in volume between arms	10 months
Bertelli et al. 1991 (23)	Electrically stimulated lymphatic drainage, two 2-week cycles with 5-week break between + elastic sleeve	34	Elastic sleeve	34	9	2 m	6 months	Difference between arms in circumference >10cm and <20 cm (summed over 7 points)	Not reported
Medical therapy as treatment for lymphedema									
Casley-Smith et al. 1993 (24) crossover	Coumarin (5,6-benzo-[α]-pyrone) (400 mg once a day for 6 months)	18	Placebo	13	24	6 months	None	'moderately severe to severe grade 2'	8 years (mean)

Trial	Experimental treatment	N	Control treatment	N	Duration of therapy (weeks)	First outcome assessment (week)	Subsequent outcome assessments	Definition of lymphedema	Duration of lymphedema (median)
Piller et al. 1988 (25) crossover	0-(β-hydroxyethyl)-rutosides (1000 mg 3X a day for 6 months)	13	Placebo	13	24	1 months	2-6 months	Grade III by International Society for Lymphology criteria, 'not spontaneously reversible by …elevation, compression, etc.'	6.6 years (mean)
Loprinzi et al. 1999 (26) crossover	Coumarin (5,6-benzo-[α]-pyrone) (200 mg twice a day for 6 months)	67	Placebo	71	24	2 months	4-6 months	'not immediately reversible by elevation or compression of the arm'	1-2years: 31% >2years: 69%
Pecking et al. 1997 (19)	Daflon (500 mg twice a day for 6 months)	51	Placebo	53	24	6 months	none	'mild to severe'	3.2 years
Physical therapy as prophylaxis for lymphedema									
Pecking et al. 1988 (27)	Active arm 1: Lymphatic drainage D1-beginning of RT, time not stated Active arm 2: Compression adhesive bandagesD1-beginning of RT, time not stated	NA*	No treatment	NA*	Day after surgery to start of RT	Day 5 after surgery	Prior to RT; 6 months, 5 years post RT	Not reported	none

*50 patients randomized, 10 excluded.

Table 3. Results of randomized trials of therapy for lymphedema.

Trial	Intervention	Response rate* n (%)	Mean reduction in arm volume from baseline	Improvement of symptoms
Hornsby 1995 (18)	Compression sleeve + exercise/massage Exercise & self-massage	12 (86%) p=0.042** 4 (36%)	Not reported	Not reported
Andersen et al. 2000 (20)	MLD + self massage +standard therapy Standard therapy: compression garment, education, exercise	Not reported	48% [95%CI 32-65%]*** 60% [95% CI 43-78%]*** p = n.s.	no significant difference between groups
Dini et al. 1998 (21)	Intermittent pneumatic compression No treatment	10 (25%) 8 (20%)	1.9 (±3.7) cm 0.5 (±3.3) cm p = n.s.	Not reported
Johansson et al. 1998 (22)	Sequential pneumatic compression MLD	Not reported	28ml 75ml p = 0.11	no significant difference between groups
Bertelli et al. 1991 (23)	Electrically stimulated lymphatic drainage Elastic sleeve	13 (38%) 10 (29%)	"About 17% in both groups"	Not reported
Casley-Smith et al. 1993 (24)	5,6- benzo-α-pyrone Placebo	Not reported	35 (±0.42)%***¶ p<0.001 41 (±0.43)%***¶	48 p<0.001 3
Piller et al. 1988 (25)	0-αhydroxyethyl-rutosides Placebo	Not reported	Not reported P<0.01, in favour of drug	28 12 p< 0.05
Loprinzi et al. 1999 (26)	Coumarin Placebo	Not reported	Increased by 58ml Increased by 21ml p = 0.8	no significant difference between groups
Pecking et al. 1997 (19)	Daflon Placebo	Not reported	"no significant differences"	Discomfort score: 4.7 (SD=1.9) 4.8 (SD = 2.1)p = n.s.
Pecking et al. 1988 (27) [prophylaxis]	 MLD Compression–adhesive bandages No treatment	% with lymphedema: 30% 55% 45%	Not reported	Not reported

Notes: MLD, manual lymphatic drainage; SD, standard deviation.

* Response rate, patients with reduction in swelling;

** Reviewer's calculation, Fisher's exact test (1-tailed);

*** Reduction in difference between normal and affected arm

¶ Mean % of normal calculated by volume of edematous arm/volume of normal arm.

Summary of the Study Results

A detailed discussion of the results of each study is presented below, categorized by the interventions being evaluated. A summary appears in Table 3 above.

Compression garments/elastic sleeve versus no treatment (one trial)

Pecking et al. 1988 compared the prophylactic use of a compression garment to no treatment as part of a randomized trial with one control and two treatment groups (27). Rates of edema were 55% with compression garments versus 45% for no treatment. Time to development of edema was similar in the two groups (16.6 months for compression garment versus 17.3 months for no treatment).

Compression garments + self massage versus self-massage (one trial)

Hornsby evaluated the addition of compression garments to standard therapy in women referred to a lymphedema clinic (18). Patients in the experimental treatment group were fitted with elastic compression sleeves and asked to wear them day and night. Both experimental and control patients were taught exercises and self-massage by a physiotherapist. Although treatment and follow-up was intended to last for 12 months, 32% of participants dropped out after the four-week assessment. By 16 weeks, the entire control group and half of the experimental group had left the trial.

During the first four weeks of treatment, 12 of 14 women in the experimental group and 4 of 11 in the control group showed a reduction in swelling, measured by the amount of fluid displaced from an immersion tank (odds ratio for reduction in swelling, 6.4; 95% confidence interval, 0.8 to 55.2; reviewer's calculation).

Manual lymphatic drainage (MLD) versus no treatment (one trial)

Pecking et al. compared MLD to no treatment as prophylactic treatment (27). Fewer patients developed lymphedema with MLD (30% versus 45% for no treatment) but the difference was not statistically significant. The time to development of lymphedema was 25.3 months versus 17.3 months (p=0.02), again favouring MLD.

No studies evaluated manual lymphatic drainage as a single modality versus no intervention for the treatment of established lymphedema.

Manual lymphatic drainage versus compression garment (one trial)

MLD was also compared against compression garments for the prevention of lymphedema in the study by Pecking et al. (27). Fewer patients developed lymphedema with MLD (30% versus 55% for no treatment), but the difference was not statistically significant.

Manual lymphatic drainage + self massage + compression garment, education, and exercise versus compression garment, education, and exercise (one trial)

Anderson et al. compared complex physical therapy with a less intensive active control (20). Women with lymphedema after breast cancer treatment who attended a lymphedema clinic were randomly allocated to manual lymphatic drainage (MLD) plus daily self-massage plus standard therapy or to standard therapy alone. Standard therapy included the use of compression garments in the form of custom-made sleeves and gloves providing 32-40 mm Hg of compression, education, and exercise. The duration of use of the compression sleeves each day was not specified. Anderson et al. described MLD as gentle massage that stimulates lymphagiomotoric activity. It was performed over a one-hour period eight times during two weeks. Lymphedema was measured at one and three months from baseline. The primary outcome variable was the mean percentage reduction in edema volume (i.e., the difference between the edematous and normal arm) at three months, relative to baseline.

There was a reduction in edema in both groups over a three-month period but no significant difference between treatments (60% reduction in the difference between arms from baseline for control versus 48% for MLD). There were no significant differences in symptom improvement between groups.

The protocol allowed members of the control group to crossover to MLD after three months in the trial. From this point on, all participants were followed for a further nine months. Ten of 22 control patients elected to receive MLD plus standard therapy after the three-month assessment.

Pneumatic compression pumps versus no treatment (one trial)

Dini et al. randomized women with postmastectomy lymphedema to intermittent pneumatic compression or no treatment (21). Constant pressure of 60 mmHg was applied throughout a two-hour treatment session. This was repeated five times a week, for two consecutive weeks, and constituted one cycle of treatment. After a five-week gap, the cycle was repeated. The total intervention time was therefore nine weeks, during which no concomitant physical therapy was allowed.

The average difference between arms (delta) after nine weeks was 14.1 cm for control and 14.2 cm with pneumatic compression. When post-treatment delta was adjusted for baseline value, the differences between groups was not significant (p=0.084). Twenty percent of the control patients and 25% of those who received pneumatic compression experienced reductions in lymphedema of 25% or more (p=0.59).

Pneumatic compression pump versus manual lymphatic drainage (one trial)

Johansson et al. compared pneumatic compression with manual lymphatic drainage (22). The administration of pressure on the involved arm was quite different from that used by Dini et al., described above (21). Johansson et al. used a sequential approach. Nine compression cells applied 40-60 mmHg pressure in a two-hour treatment session. This was administered five days a week, for a period of two weeks. Patients wore a compression sleeve for two weeks before randomization and were instructed to wear the sleeve during the day for the duration of the trial.

Lymphedema was reduced by 49 ml (7%) during the two-week pre-randomization phase when compression sleeves were worn. Further reductions of 75 ml in the MLD group and 28 ml in the pneumatic compression group (p=0.11) were achieved during two weeks of treatment.

Electrically stimulated lymphatic drainage + compression garment versus compression garment only (one trial)

Bertelli et al. compared electrically stimulated lymphatic drainage plus the use of a compression garment to a compression garment alone (23). Patients in both groups were instructed to wear a standard (not custom-made) elastic sleeve for six hours a day; the sleeve extended from either hand to shoulder or wrist to shoulder depending on the extent of swelling. Electrically stimulated lymphatic drainage (ESD) was used as induction therapy in the experimental group. Eight electrodes were placed between the supraclavicular region and the wrist, over lymphatic stations or motor points. A sequence of electrical impulses at 4.5 kHz was administered over 30 minutes. Therapy was applied in two cycles of ten sessions over two weeks, followed by a five-week break and another two-week cycle of therapy, giving a total treatment time of nine weeks. No other treatment for lymphedema was permitted during the trial.

The mean absolute difference (delta) between the edematous and normal arm at two months was 12.6 cm with the ESD-based experimental treatment versus 12.1 cm with control treatment. At six months from baseline (i.e., four months after the end of treatment), the mean delta values were 12.4 and 11.6 respectively. Bertelli et al. also reported response rates, where response was defined as a reduction in delta of 25% or more of the baseline value. Response

rates at two months were 38.3% with ESD and 29.4% without. None of the differences between groups were statistically significant.

Medical therapy versus placebo (four trials)

Three different medical therapies were tested in four RCTs.

Three of these were benzopyrones, compounds with the potential to stimulate proteolysis by tissue macrophages. Casley-Smith et al. (24) and Loprinzi et al. (26) used 5,6–benzo-α-pyrone (also know as coumarin). Piller et al. used O-β-hydroxyethyl-rutosides (25). Two of these trials included patients with leg edema in addition to patients with arm lymphedema from breast cancer but presented data on response to treatment separately for the two patient groups (24,25). Pecking et al. studied Daflon, a purified micronized flavonoidic fraction, whose potential mechanism of action was through improving venous tone, capillary permeability and resistance, and lymphagogue activity (19). These drugs were taken orally for six months. The participants in the RCTs of medical therapy tended to have lymphedema of greater severity for longer duration than those in the trials of physical therapies described above.

Two of three trials of benzopyrones detected statistically significant reductions in arm volume and improvements in symptoms in favour of the active drug compared with placebo (Table 3) (24,25). The third trial found no significant difference between coumarin and placebo (26). Although no serious adverse effects were reported for the first two trials (24,25), Loprinzi et al. (26) reported that nine of 140 women treated with coumarin for six months had evidence of hepatotoxicity (serum aminotransferase concentrations 2.5 times the upper limit of normal), compared with none during placebo treatment ($p<0.006$).

A randomized trial of Daflon found no significant differences in arm volume or discomfort score between Daflon and placebo (19).

V. INTERPRETIVE SUMMARY

From the randomized trials of physical therapy for lymphedema, the only positive finding was an incremental benefit when use of an elastic sleeve was added to self-massage therapy (18). Pneumatic compression, when compared with no intervention, was not associated with a significant improvement of the magnitude that the study was powered to detect (21). However, the direction of the observed response rates and changes in arm volume favoured pneumatic compression (21). None of the other, more aggressive approaches were found to have benefits when compared with less aggressive controls, although definitive statements regarding their effectiveness when compared with no intervention cannot be made. The heterogeneous outcomes that were used to measure treatment effects make synthesizing the evidence difficult.

In terms of medical therapies, there was contradictory evidence about the role of coumarin in the management of lymphedema. Casley-Smith et al. and Loprinzi et al. used very similar study designs but arrived at opposite conclusions (24,26). The fact that ongoing physical therapy appeared to be expected in the Loprinzi et al. study, while the study by Casley-Smith et al. excluded the use of physical therapy, may explain this difference. The role of O-β-rutosides is promising but requires further study (25). The data do not suggest that Daflon has clinically significant activity in the treatment of lymphedema (19).

None of the trials described significant adverse effects related to the test interventions. This should not be interpreted as evidence in support of use of therapies with no proven value. The psychological, economic, and time implications cannot be ignored.

There were no trials meeting the eligibility criteria that were designed to address the role of many recommendations commonly used in clinical practice such as the use of diuretics or non-medical therapies (such as magnetic therapy or infrared garments). As such, recommendations on their use cannot be made.

Only one trial addressed prevention of lymphedema comparing compression bandages versus lymphatic drainage. The choice of radiation therapy and surgical techniques on the prevention of lymphedema may have a more prominent role in the prevention of lymphedema compared with additional interventions.

VI. ONGOING TRIALS

Although no ongoing trials addressing the management of lymphedema were identified during the literature search, the authors are aware of an active trial by the Ontario Clinical Oncology Group (OCOG) that began accruing patients in February 2003. The OCOG (DELTA) trial entitled, *"A randomized trial of decongestive lymphatic therapy for lymphedema in women with breast cancer"* is designed to address the role of massage (decongestive) therapy by randomly allocating patients to receive either massage and bandaging followed by compression sleeve or compression sleeve alone. Outcomes: arm volume, infection rate, quality of life, and other lymphedema-related symptoms. Projected accrual: 100 breast cancer patients from three regional cancer centres over the next 1-2 years.

VII. FUTURE RESEARCH

Further studies are required to address the role of physical-therapy-based interventions, alone or in combination with other treatment modalities. Fundamental to the interpretation of the evidence are two key methodological issues that require definition to facilitate future research.

1. What is the current standard therapy? Reaching consensus among clinicians and researchers as to what constitutes the 'standard' clinical approach for established lymphedema would be useful. It should be kept in mind that the effects of complex physical therapy and pneumatic compression will not be sustained unless they are complemented with compression bandaging or sleeves.
2. Which outcomes are clinically relevant? Consensus on the important outcomes to be measured, and how to define them in clinical trials, is important. These could include parameters such as the proportion of patients with response, symptom scores, adverse effects, and compliance.

From a measurement perspective, arm volume should be calculated. This method of documenting lymphedema is clinically feasible and gives a better picture of the absolute volume of the lymphedema than do circumference measurements (28). Five-point measurement in both the affected and control limb, as well as hand measurement that include several fingers, has been advocated.

Definitions for the classification of lymphedema such as mild (<250 ml), marked (250-500ml) or severe (>500ml) have been recommended. Validation of these definitions against symptom profiles and patient perceptions could be useful.

From a clinical perspective, the measurement of morbidity related to lymphedema, using tools such as lymphedema-specific quality of life, symptom measurement instruments, and functional assessments would provide a more comprehensive assessment. Studies based on these outcomes are more likely to influence clinical practice.

VIII. OPINIONS OF THE SUPPORTIVE CARE GUIDELINES GROUP

The lack of sufficient high quality evidence precludes definitive recommendations being made. Instead, the SCGG offers the following opinions based on the evidence reviewed:

- There is some evidence which suggests that physical therapies such as compression therapy and manual lymphatic drainage may improve established lymphedema but further studies are needed.
- There is no current evidence to support the use of medical therapies, including the use of diuretics, in the management of lymphedema.

- Additional efforts to define relevant clinical outcomes to use for the assessment of patients with lymphedema would be valuable.
- The SCGG endorses the recommendations from the Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. The use of compression garments, as recommended in the national guideline, is consistent with what is commonly practiced clinically.
- The recommendations are appropriate for patients with more than mild lymphedema, where the signs and symptoms are considered significant from the patients' perspective.
- There is insufficient evidence to support an evidence-based recommendation on which to base a practice guideline for the treatment of lymphedema. Available studies were uniformly small and underpowered, limiting the power of inference.
- Compression garments should be worn from morning to night and removed at bedtime. Patients should be informed that lymphedema is a lifelong condition and that compression garments must be worn on a daily basis. Patients can expect stabilization and/or modest improvement of edema with the use of the garment in the prescribed fashion.

Review of the National Lymphedema Guideline

The SCGG reviewed the national guideline on lymphedema in detail (6). In the national guideline, the Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer provided six recommendations, four of which were pertinent to the treatment of lymphedema:

1. Practitioners may want to encourage long-term and consistent use of compression garments by women with lymphedema.
2. One randomized trial has demonstrated a trend in favour of pneumatic compression pumps compared with no treatment. Further randomized trials are required to determine whether pneumatic compression provides additional benefit over compression garments alone.
3. Complex physical therapy, also called complex decongestive physiotherapy, requires further evaluation in randomized trials. In one randomized trial, no difference in outcomes was detected between compression garments plus manual lymph drainage versus compression garments alone.
4. Clinical experience supports encouraging patients to consider some practical advice regarding skin care, exercise, and body weight.

Recommendation 1 from the national Steering Committee was based on response rates from a single-cohort study and from a randomized trial of electrically stimulated lymphatic drainage plus a compression garment versus the compression garment alone (23). While the data are limited, there are no significant adverse effects associated with this compression garment. The SCGG supports the national recommendation on compression garments, taking into account evidence from a single, small randomized trial by Hornsby (18) of compression garments plus exercise and self-massage versus exercise and self-massage. The use of compression garments is frequently recommended in standard clinical practice in Ontario.

Recommendations 2 and 3 from the national Steering Committee are based on evidence from a limited number of RCTs. The SCGG agrees that the use of pneumatic compression pumps and other more novel strategies such as complex physical therapy would benefit from further study.

Recommendation 4 is based on what is considered to be current clinical practice. These approaches are commonly incorporated into care, in addition to the interventions evaluated in clinical trials.

The SCGG observed that much of the evidence included in the national guideline came from case series and non-randomized studies. While the national guideline included most of the

evidence available, it is the opinion of the SCGG that the existing evidence is not sufficiently strong enough to permit the formulation of evidence-based treatment guidelines. The recommendations are clinically sensible and provide reasonable guidance to practitioners. The SCGG elected to prepare a summary of the evidence from randomized trials for use by practitioners in Ontario to supplement the national practice guideline.

IX. EXTERNAL REVIEW OF THE EVIDENCE SUMMARY REPORT

Practitioner Feedback

A draft version of this report was reviewed by Ontario practitioners and non-physician health care professionals. Any changes made to the report as a result of practitioner feedback are described in the "Modifications" section below.

Methods

Practitioner feedback was obtained through a mailed survey of 287 practitioners in Ontario (107 medical oncologists, 45 radiation oncologists, and 135 surgical oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. The practitioner feedback survey was mailed out on September 25, 2002. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The SCGG reviewed the results of the survey and decided to mail the survey to an additional group of health care professionals. The same survey was mailed out to 52 non-physician health care professionals (22 nurses, 19 physiotherapists, and 11 other health care professionals with specific interest in the management of lymphedema) on December 5, 2002. Additional mailings followed the schedule as outlined above. The SCGG reviewed the results of both surveys.

Results of PF Mailing to Oncologists

158 responses were received out of the 287 surveys sent to oncologists (55% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 125 indicated that the report was relevant to their clinical practice and completed the survey. Three respondents left that question unanswered but responded to the rest of the questionnaire. Key results of the practitioner feedback survey for oncologists are summarized in Table 4a.

Table 4a. Practitioner feedback survey results for oncologists.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	125 (97%)	2 (2%)	1 (1%)
There is a need for an evidence summary on this topic.	105 (82%)	20 (16%)	3 (2%)
The literature search is relevant and complete in this evidence summary.	115 (91%)	11 (9%)	1 (1%)
I agree with the methodology used to summarize the evidence.	121 (95%)	5 (4%)	1 (1%)
I agree with the overall interpretation of the evidence in the evidence summary.	122 (95%)	5 (4%)	1 (1%)
The Opinions of the Disease Site Group section of this evidence summary is useful.	105 (84%)	16 (13%)	3 (2%)
An evidence summary of this type will be useful for clinical decision making.	86 (68%)	33 (26%)	6 (5%)
At present, there is insufficient evidence to develop a practice guideline on this topic.	97 (77%)	16 (13%)	13 (10%)
There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available.	107 (86%)	13 (10%)	2 (2%)
Do you believe that the evidence supports the use of compression therapies in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	74 (59%)	31 (25%)	21 (17%)

Results of PF Mailing to Health Care Professionals

33 responses were received out of the 52 surveys sent to non-physician health care professionals (63% response rate). Of those who responded, 25 health care professionals indicated that the report was relevant to their clinical setting and completed the survey. In total, 28 health care professionals completed the survey. Key results for this group are summarized in Table 4b.

Table 4b. Practitioner feedback survey results for health care professionals.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	27 (96%)	1 (4%)	0
There is a need for an evidence summary on this topic.	26 (93%)	2 (7%)	0
The literature search is relevant and complete in this evidence summary.	13 (54%)	7 (29%)	4 (17%)
I agree with the methodology used to summarize the evidence.	21 (78%)	6 (22%)	0
I agree with the overall interpretation of the evidence in the evidence summary.	21 (78%)	3 (11%)	3 (11%)
The Opinions of the Disease Site Group section of this evidence summary is useful.	22 (92%)	0	2 (8%)
An evidence summary of this type will be useful for clinical decision making.	23 (82%)	2 (7%)	3 (11%)
At present, there is insufficient evidence to develop a practice guideline on this topic.	23 (82%)	3 (11%)	2 (7%)
There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available.	28 (100%)	0	0
Do you believe that the evidence supports the use of compression therapies in your own practice?	**Rated "strongly agree" or "agree"**	**Rated "neither agree nor disagree"**	**Rated "disagree" or "disagree strongly"**
	20 (71%)	8 (29%)	0

Summary of Written Comments (Oncologists)

Forty-eight oncologists (38%) provided written comments. The main points contained in the written comments were:

General comments

1. Several practitioners felt that the evidence summary confirmed that lymphedema is a difficult problem to deal with effectively. Several also agreed that there is insufficient evidence available at this time for a practice guideline and commented that more research is needed on this topic.
2. Several practitioners commented that the evidence summary was clear, well written, well documented, and interesting.
3. One practitioner commented that despite the lack of good evidence supporting specific therapies, the importance of guidelines cannot be underestimated. He/she found it helpful to know that there is no single specific intervention in dealing with these patients.
4. Three practitioners commented that lymphedema is not a significant problem in their practice.

Rationale and scope of evidence summary

5. Two practitioners commented that the severity of lymphedema and its implications on choice of intervention is not well addressed. Suggestions to include classification of severity of lymphedema and methods of measuring lymphedema and outcome assessment were made.
6. Two practitioners suggested that the literature related to prevention be addressed; however, it was noted that this may not be appropriate within the context of the current evidence summary.
7. One practitioner commented that the biggest risk for lymphedema is the combination of surgery plus axillary radiation.
8. One practitioner inquired whether use of the sentinel node biopsy is associated with lower incidence of lymphedema and if so, he/she felt that the issue should be discussed.

9. One practitioner suggested that recommendations for general care (i.e. skin care, impact of weight bearing bones, avoidance of blood sampling, avoidance/prompt treatment of infection) be incorporated in the evidence summary.
10. One practitioner commented that evidence on the use of diuretics should be considered.
11. One practitioner asked about the role of microvascular surgery in the management of lymphedema.
12. One practitioner queried about the role of vacuum assisted closure (VAS) in lymphedema management, given that this has been used effectively in flap microsurgery in complex wound management.
13. One practitioner suggested that non-medical literature be searched to address therapies such as magnetic therapy and far-infrared garments

Application of the evidence

14. Three practitioners commented that compression garments are used in their practice as they are harmless. However, one of these practitioners commented that it should be stated that the evidence is limited and that clinical trials to obtain level I evidence should be encouraged.
15. One practitioner stated that he/she will continue to use compression therapy because patients repeatedly say that it helps.
16. Several practitioners felt that compression has an important role in the management of lymphedema.
17. One practitioner commented that this is a common and distressing problem for patients and close relatives because it is so obvious. The practitioner noted that both patients and practitioners often feel compelled to try anything whatever the evidence.

Editorial comments

18. A suggestion was made to replace the term “medical therapies” with “drug therapies” or “drugs”.
19. Two practitioners suggested including a comment that all studies were generally small and underpowered, therefore limiting the strength of the evidence.
20. One practitioner suggested describing how the incremental benefit was measured in the small randomized trial mentioned in the first bullet.
21. It was also noted that two of the bullets in the Conclusions are somewhat contradictory. The practitioner felt that this discrepancy needs to be resolved.
22. One practitioner felt that treatment is not always needed (although the evidence summary gives the impression that it is), particularly in cases of mild lymphedema.
23. One practitioner felt that a statement regarding potential for harm should be included.

Modifications/Actions

1-4. Modifications were not required in response to these comments.

5. Severity of lymphedema as eligibility criteria for each of the included trials was tabulated in Table 2. Validation of the definitions of lymphedema, methods of measuring lymphedema, and methods of measuring outcomes is beyond the scope of this evidence summary. The SCGG agree that standardization of these parameters is strongly encouraged in future studies.

6-8. Prevention of lymphedema addresses a related but different topic. The effect of different surgical techniques or radiotherapy techniques is related but goes beyond the primary focus of this report. A comment to this effect is included in the Interpretive Summary. A comment on risk factors for lymphedema, such as axillary node dissection and sentinel node biopsy, was added to the Choice of Topic and Rationale section.

9-13. Recommendations on the use of diuretics, general skin care issues, vacuum-assisted closure, microvascular surgery, and non-medical therapies such as magnetic therapy and infrared garments cannot be made due to a lack of sufficient evidence on these

topics. A statement to this effect was added to the Interpretive Summary section of the document.

14-17. No modifications required in response to these comments.

18. The term was modified as per the practitioner's suggestion.

19. A statement was added to the Opinions section in response to this suggestion.

20. The magnitude of difference detected within the studies is tabulated in Table 3. Validation of the clinical significance of these differences is beyond the scope of this evidence summary. The SCGG strongly supports the need for incorporated study design intended to detect validated clinically significant differences in future study design.

21. The Conclusions section was changed to the Opinions of the SCGG. A statement was inserted to clarify that although there is insufficient evidence to support an evidence-based recommendation for a practice guideline, the SCGG endorses the recommendations from the Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer.

22. The wording of the fifth statement in the Opinions section was modified in response to the practitioner's comment.

23. None of the trials described adverse effects from the study therapy. Potential harms in adopting unproven therapies such as psychosocial, economic, and time were added to the Interpretive Summary.

Summary of Written Comments (Health Care Professionals)

Twenty-three non-physician health care professionals (82%) including physiologists, nurses, and physiotherapists provided written comments. The main points contained in the written comments were:

General comments

1. One lymphatic scientist, involved with other scientists and clinicians interested in lymphedema agreed that the benefits of current therapies are unproven.

Rationale and scope of evidence summary

2. One respondent felt that the Target Population section should be revised since anyone who has been diagnosed with lymphedema has symptoms and should receive treatment.
3. Three comments stressed the need for practical advice concerning skin care, exercise, and maintenance of a healthy body weight. One respondent also questioned whether evidence on sentinel node biopsy and the incidence of lymphedema exists. This respondent suggested correlating surgical procedures to the incidence of lymphedema.

Methods

4. Seven respondents commented that the limitation to English language articles was too restrictive.
5. One respondent questioned the wisdom of limiting the search to randomized trials and wondered whether physiotherapy journals were reviewed.

Results

6. Three professionals felt that the issue of quality of life needed to be addressed.

Interpretive summary

7. One respondent disagreed with one of the statements on manual lymphatic drainage and said that massage typically starts at the neck, progressing to the contralateral trunk side, and then to the edematous trunk and extremity. He/she also noted that CDT patients are seen daily for 4-6 weeks before fitting with a compression garment.
8. In the practice of compression therapy with pump, one respondent disagreed with the suggestion that the pump is stopped after one month. Rather, it was suggested that the pump be continued until plateau is reached. The respondent felt that more details are

required with respect to this practice regarding daily use and the amount of pressure applied.

Opinions

9. Four respondents expressed concern about the first statement in the Opinions section and commented that physicians might be inclined to tell patients that nothing can be done. It was suggested that other methods of supportive care such as education and general skin care advice be included in this section.

Application of results

10. Six comments reflected agreement that more and better designed trials are required to evaluate all types of compression including compression pumps, bandaging, and garments as well as the effectiveness of complete decongestive therapy and manual lymph drainage.
11. Two comments mentioned the need for education of medical professionals in recognizing and treating lymphedema as well as the prophylactic education of patients.
12. A comment was made that further research is also needed on different types of massage.
13. It was suggested that a database be established in Ontario such that the incidence of lymphedema in cancer patients can be tracked.
14. Two respondents stressed the need for consistency in terms of defining and measuring lymphedema and also clinically relevant outcome measures.

Modifications/Actions

1. No changes were made in response to this comment.
2. The authors feel that not all patients with lymphedema are symptomatic and require treatment.
3. Recommendations on the effect of exercise and body weight cannot be made in the absence of evidence. Comments to this effect have been included in the Interpretive Summary.
4. Due to limited resources available for translation, the PEBC typically limits searches to English language articles. However, in response to the comments made, non-English articles will be included in the next update for this evidence summary.
5. All journals indexed in Index Medicus were included in the literature search. There were no specific exclusions in terms of journal type.
6. Quality of life was included as one of the outcomes of interest. No data were available from the included studies.

7 & 8. The evidence summary did not provide specific recommendations on how to deliver MLD. The descriptions provided for specific procedures are as described in the original studies.

9. The authors feel the opinions as written are a fair representation of the limited strength of the evidence around physical therapies as presented within the document.

10-14. The authors agreed with the comments made and hope that the evidence summary provides impetus for researchers to conduct further research in this area.

Practice Guidelines Coordinating Committee Approval Process

The evidence summary report was circulated to thirteen members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eight of thirteen members of the PGCC returned ballots. Six PGCC members approved the evidence summary report as written, one member approved the report with modifications, and one member approved the report and offered a suggestion for consideration by the SCGG. The required modifications included rewording the first two bullets in the Opinions section and offering an additional opinion on the practical issues of frequency of physical therapies, duration of therapy, and the expectations for improvement. The PGCC also suggested including a comment on the

role of diuretics. A final suggestion was made to include an active randomized trial on manual lymphatic drainage in the ongoing trials section of the report.

Modifications/Actions

The SCGG agreed with the stylistic and grammatical suggestions of the PGCC and modified the first two bullets in the opinions section. A statement was also made that there is no current evidence to support the use of diuretics. An additional opinion was offered on the practical issues outlined above. A brief description of the OCOG trial on manual lymphatic drainage was added to the ongoing trials section of the evidence summary.

X. CONCLUDING REMARKS

In summary, feedback from nurses, physiotherapists, and oncologists from the external review process confirms that there is a need for an evidence summary on this topic and that the lack of evidence at this time precludes definitive recommendations. When sufficient evidence becomes available, there is great interest in the development of an evidence-based practice guideline. In light of current evidence, it is the Supportive Care Guideline Group's opinion that lymphedema patients may benefit from the use of physical therapies such as compression therapy and manual lymphatic drainage. According to the results of the external review process, this opinion is consistent with current practice among the majority of oncologists and non-physician health care professionals in Ontario.

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XII. ACKNOWLEDGMENTS

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For a complete list of Supportive Care Guidelines Group members and the Practice Guidelines Coordinating Committee members, please visit our web site at http://www.cancercare.on.ca/access_PEBC.htm.

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